A STUDY OF THE REACTION OF TETRAALKYLMETHYLENEDIAMINES WITH ACTIVE HYDROGEN COMPOUNDS

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By

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PREFACE

The research presented in this dissertation was carried out under the sponsorship of the Office of Ordnance Research. This material was presented in part at the National Meeting of the American Chemical Society at New York in September 1954.

SECTION I

INTRODUCTION

A. Literature Review

In 1917 Mannich[1] first reported the reaction which now bears his name. He prepared beta-ketonic bases by means of the reaction between acetone or diethylketone, 35% formaldehyde solution, and ammonium salts, or the hydrochloride of methylamine or dimethylamine. The description of the reaction by Blicke[2] has been expanded to include the condensation of ammonia or a primary or secondary amine, usually as the hydrochloride, with formaldehyde and a compound containing at least one hydrogen atom of pronounced reactivity.

Bruson and Butler[3] have shown that 2, 4, 6-trinitrotoluene will undergo the Mannich reaction with amines and formaldehyde, although these authors did not attempt to propose a mechanism. It is of interest to note that the free amines were used rather than the amine hydrochloride.

Substituted aminomethanols were found by Henry[4] to react with nitroethane to replace both of the alpha-hydrogens of the nitroethane with dialkylaminomethyl groups. Similar results were obtained

by Duden, Bock, and Reid.[5] Henry[6] observed that dialkylaminomethanols reacted readily with secondary aliphatic and hetrocyclic amines. Zief and Mason[7] attempted to react 1-morpholinomethanol with acetonitrile, propionitrile, butyronitrile, and phenylacetonitrile. They found that reaction occurred only with the phenylacetonitrile. This reaction was not described by the authors as being the Mannich reaction. Senkus[8] and Johnson[9] prepared a series of compounds by reaction of primary and secondary aliphatic amines and aromatic amines with formaldehyde and nitroparaffins. These authors were able to produce the same products by the following reaction sequences:

(1) $R_2NH + HCHO \longrightarrow R_2NCH_2OH$

$R_2NCH_2OH + R_2CHNO_2 \longrightarrow R_2NCH_2C(NO_2)R_2 + H_2O$

(2) $R_2CHNO_2 + HCHO \longrightarrow R_2C(NO_2)CH_2OH$

$R_2C(NO_2)CH_2OH + R_2NH \longrightarrow R_2NCH_2C(NO_2)R_2.$

Johnson[9] stated that the work described did not give sufficient evidence for establishing the mechanism of the reaction. However, he did suggest that when nitroalcohols were used, the first step probably was:

$$R_2C(NO_2)CH_2OH \xrightarrow{OH^-} HCHO + R_2CHNO_2$$

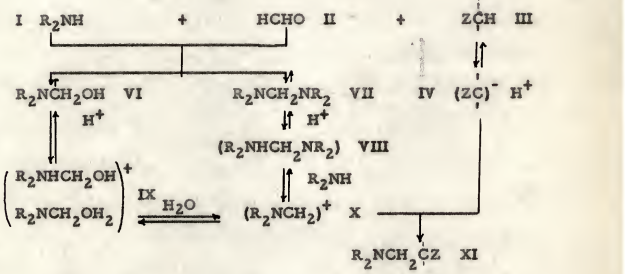
followed by reaction of the amine with the formaldehyde. He also

stated that "The reaction of N-hydroxymethylamines with a nitroparaffin is similar to the Mannich reaction in which the active hydrogen is furnished by the aldehyde or ketone rather than the nitroparaffin."

Although Mannich[1] did not work with nitroparaffins, he did not restrict his work to active hydrogens of aldehydes and ketones. Blicke[2] included the reaction of ammonia, primary or secondary amines with formaldehyde and any compound containing at least one hydrogen atom of pronounced reactivity under his discussion of the Mannich reaction. However, many of the examples cited gave better yields when the amine was introduced in the form of its hydrochloride rather than as the free amine. The only example cited in which a basic catalyst appeared to be beneficial was the reaction of 2, 4, 6-trinitrotoluene with secondary amines and formaldehyde by Bruson and Butler.[3] Zief and Mason[7] used potassium carbonate as the catalyst when morpholine and formaldehyde reacted with phenylacetonitrile. Johnson[9] found that basic catalysts were beneficial when weakly basic amines such as aromatic amines reacted with formaldehyde and nitroparaffins; although, as pointed out above, this author did not consider this reaction as an example of the Mannich reaction, but merely stated that the reactions were similar. Butler and McMillan[10] have shown that improved yields were obtained in a much shorter time when basic catalysts were added to the reaction mixture of secondary amines, formaldehyde, and nitroparaffins. In contrast, Alexander and Underhill[11] have shown that the

Mannich reaction of ethylmalonic acid, formaldehyde, and dimethylamine occurs only between the pH ranges of about one to seven. No work has been reported in which the reaction of an amine hydrochloride with formaldehyde and nitroparaffins was attempted; however, Wiley and Behr[12] have shown that 2, 4, 6-trinitrotoluene will react with secondary amine hydrochlorides and formaldehyde.

A possible mechanism for the Mannich reaction was proposed by Lieberman and Wagner.[13] Schematically this would be:

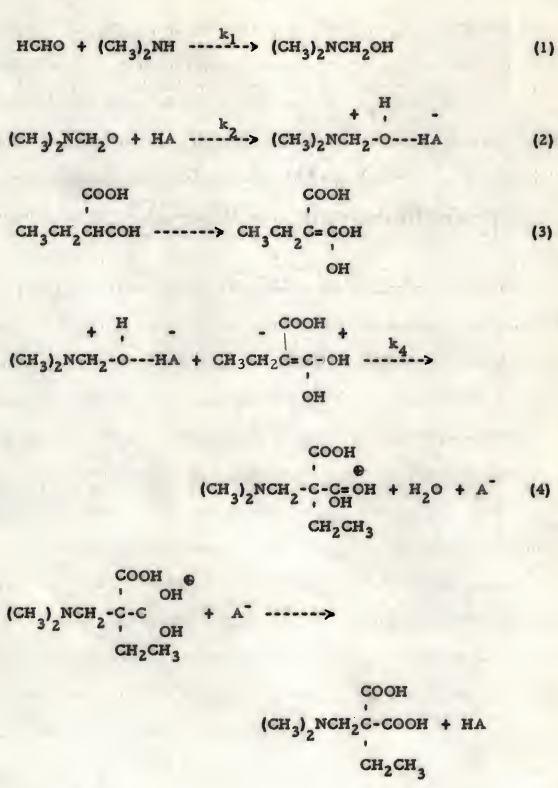


The authors also stated that "The optimum acid-base relationships in any case, and the advisability or admissibility of adding acid or alkali, depend upon the basic character of I and the acidic character of III. The results reported point to the conclusions (a) that with increasing basicity of I the favorable influence of acid, and the amount that may

be added profitably decreases and that of alkali increases, (b) that with increasing acidity of III the favorable influence of acid decreases and that considerable initial acidity may give maximum yields in reasonable periods only if a compensatory increase in the amount of an initial reactant is made during or at the outset of the reaction, or if the concentration of acid is progressively decreased by neutralization as reaction proceeds."

It has been shown by Fieldman and Wagner[14] that Mannich bases can be obtained by reacting tetraalkylmethylenediamines with phenols. They have shown also that the phenols will react with amines and formaldehydes. Logan and Huston[15] reacted C^{14}-labeled paraformaldehyde with dimethylamine hydrochloride and acetophenone. They found that there was no transposition of carbon atoms during the formation of the Mannich base.

Kinetic studies were made by Alexander and Underhill[11] using ethylmalonic acid, dimethylamine, and formaldehyde. They found that the reaction was first order in each component, and third order over all. It was also observed that the rate was critically dependent on pH, and that it passed through a maximum at about pH 3.8. From their results, they proposed the following mechanism:


HCHO + (CH3)2NH ---k1--> (CH3)2NCH2OH (1)
(CH3)2NCH2O + HA ---k2--> (CH3)2NCH2-O---HA (2)
CH3CH2CHCOH -------> CH3CH2C=COH (3)
(CH3)2NCH2-O---HA + CH3CH2C=C-OH ---k4-->
(CH3)2NCH2-C-C=OH + H2O + A- (4)
(CH3)2NCH2-C-C + A- ------->
(CH3)2NCH2C-COOH + HA

The experimental results indicated that the methylol compound was formed first, since they were able to obtain smooth third order curves only after allowing the amine and formaldehyde to stand together for twelve hours. The same rate constant was obtained using the methylol compound as with the separate starting materials. They were unable to obtain a reaction between formaldehyde and ethylmalonic acid.

The results of Grillot and Bashford[16] contradict the suggestion of Alexander and Underhill[11] that enolization is a step in the mechanism of the Mannich reaction. They found that the reaction of d- and l-o-nitromandelic acids with formaldehyde and piperidine gave Mannich bases as products whose rotations were higher than the rotation of the starting optically active mandelic acids. However, there is some doubt as to the validity of this part of their work. Meinwald and Hutto[17] found that a Mannich base had not actually been produced. Instead, it was simple salt formation that had occurred. From the fact that acetophenone underwent the Mannich reaction, while they were unable to get the somewhat hindered alpha-methylbutyrophenone to react, they have suggested an S_N2 mechanism for the Mannich reaction rather than an ionization followed by a rapid union of the resulting carbonium ion with the alkylaminomethyl group.

By reacting secondary amines, formaldehyde, and alcohol, McLeod and Robinson[18] were able to isolate ethers of the type

R_2NCH_2OR'. They represented this process by

$$R_2NH + HCHO \text{ -------> } (R_2NCH_2OH \text{ <------> } R_2N{=}CH_2^{+}\ OH^{-})$$

$$R_2N{=}CH_2^{+}\ OH^{-} + R'OH \text{ -------> } R_2NCH_2OR' + H_2O.$$

They found that these ethers could be condensed with active hydrogen compounds.

B. Statement of the Problem

Possible mechanisms for the Mannich reaction have been suggested by Alexander and Underhill[11] and by Lieberman and Wagner.[13] Although much useful information has been acquired from their work, the mechanism of the Mannich reaction has not yet been definitely established.

Thus, it was decided to investigate further the reaction of tetraalkylmethylenediamines with active hydrogen compounds. It was thought that the use of radioactive tracer techniques would prove to be useful.

C. Source and Purification of Reactants

The diethylamine obtained from Carbide and Carbon Chemicals Corporation and the formalin obtained from Columbia Organic Chemicals

Company, Incorporated were used without further purification in the preparation of tetraethylmethylenediamine.[19] The tetraethylmethylenediamine was then used with 2-nitropropane obtained from Commercial Solvents Corporation in the preparation of 1-diethylamino-2-methyl-2-nitropropane. Another active hydrogen compound that was used as received was p-nitrophenylacetonitrile obtained from Distillation Products Industries.

Ethyl benzene which was obtained from the Dow Chemical Company was used without further purification in the preparation of 2,4-dinitroethylbenzene. Ethyl acetoacetate which was obtained from Carbide and Carbon Chemicals Corporation was redistilled before it was used in the preparation of ethyl nitroacetate.

The formaldehyde-C^{14} and sodium cyanide-C^{14} were obtained from Isotopes Specialties Company. One millimole of formaldehyde had an activity of one millicurie and it was dissolved in ten milliliters of water. One-third of a millimole of sodium cyanide had an activity of one millicurie.

SECTION II

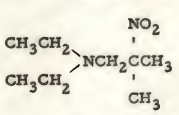
PREPARATION OF MANNICH BASES

A. Discussion

During the course of this study, several new Mannich bases were prepared. In most cases, the active hydrogen compound was reacted with tetraethylmethylenediamine in the absence of solvent. The active hydrogen compounds that were used were 2-nitropropane, p-nitrophenylacetonitrile, 2, 4-dinitroethylbenzene, and ethyl nitroacetate. An attempt to prepare 2, 4-dinitroethylbenzene by the method of Borsche[20] proved unsuccessful. It was successfully prepared by a modification of the procedure for the preparation of dinitrodurene.[21] The method described by Rodionov, Machinskaya, and Belikov[22] for the preparation of ethyl nitroacetate not only did not work, but the physical constants described were also incorrect. By using the method described by Bouveault and Wahl,[23] it was possible to prepare ethyl nitroacetate.

B. Experimental

Preparation of 1-Diethylamino-2-methyl-2-nitropropane



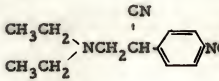
In a 500 ml., round-bottomed, three-necked flask equipped with a mechanical stirrer and a reflux condenser were placed 79.2 gms. of tetraethylmethylenediamine (0.5 mole), 44.5 gms. of 2-nitropropane, and 100 ml. of water. The materials were heated with stirring for a period of four hours on a steam bath. On cooling, the two layers were separated mechanically, and the aqueous portion was extracted three times with benzene. The combined organic portion and benzene extracts were distilled using a Claisen flask. A yield of 32.3 gms. of 1-diethylamino-2-methyl-2-nitropropane was obtained at a temperature of 90-2° and a pressure of 10 mm. This represented 37.1% of the theoretical.

Analysis:

	%C	%H	%N
Calculated	55.14	10.41	16.08
Observed*	54.92	9.95	15.93

*All carbon, hydrogen, and nitrogen analyses were done by Peninsular ChemResearch, Inc.

Preparation of
3-Diethylamino-2-(p-nitrophenyl)propionitrile

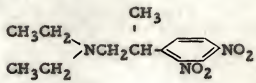


Seven and nine-tenths grams of tetraethylmethylenediamine (0.05 mole) and 8.2 gms. of p-nitrophenylacetonitrile (0.05 mole) were placed in a 28 x 190 mm. test tube equipped with an air cooled condenser. Heating on the steam bath was carried out over a three hour period. The material in the test tube at first became purple and later blue. On cooling, a red liquid which had the odor of diethylamine was poured off leaving a dark green amorphous solid. The red solution was later shown to be a solution of the Mannich base in diethylamine. Attempts to crystallize the Mannich base from acetone, alcohol, chloroform, benzene, and water were unsuccessful.

Analysis:

	%C	%H	%N
Calculated	63.24	6.93	16.99
Observed	63.11	6.79	16.94

Preparation of
1-Diethylamino-2-(2, 4-dinitrophenyl)-propane



Three and four-tenths grams of tetraethylmethylenediamine (0.0214 mole) and 4.2 gms. of 2, 4-dinitroethylbenzene (0.0214 mole) were placed in a 28 x 190 mm. test tube equipped with an air cooled condenser. The immiscible materials became miscible on warming. Heating on the steam bath was carried out over a two hour period. Purification by means of vacuum distillation from a Claisen flask yielded 1.7 gms. of the dark red liquid Mannich base. This represented 28.3% of the theoretical. Considerable product was lost due to decomposition during the distillation.

Physical Constants:

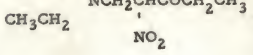
D_{20}^{20} 1.268

B. P. . . . . 190° at 5 mm. (decomp.)

Analysis:

	%C	%H	%N
Calculated	55.50	6.81	14.94
Observed	55.40	6.71	14.58

Preparation of
Ethyl 3-Diethylamino-2-nitropropionate



Five grams of ethyl nitroacetate (0.0376 mole) and 5.9 gms. of tetraethylmethylenediamine (0.0376 mole) were placed in a 28 x 190 mm. test tube. The reaction mixture became warm immediately and darkened. After cooling, the diethylamine which had been formed in the reaction was removed under vacuum leaving a viscous oil. On standing this oil partially crystallized. When no further solid crystallized, the viscous oil which surrounded it was washed away with ether leaving an orange colored solid which melted at 109-11°. Further attempts to purify the compound from ethanol, benzene, dioxane, water, heptane, and by distillation were unsuccessful. The yield of the Mannich base was 2.6 gms. This was 31.7% of the theoretical.

Analysis:

	%C	%H	%N
Calculated	49.53	8.31	12.84
Observed	49.35	8.21	12.73

TABLE I

ANALYTICAL DATA ON MANNICH BASES

Mannich Base	Empirical Formula	% Carbon		% Hydrogen		% Nitrogen	
		Calc.	Obs.	Calc.	Obs.	Calc.	Obs.
1-Diethylamino-2-methyl-2-nitropropane	$C_8H_{18}N_2O_2$	55.14	54.92	10.41	9.95	16.08	15.93
3-Diethylamino-2-(p-nitrophenyl)propionitrile	$C_{13}H_{17}N_3O_2$	63.24	63.11	6.93	6.79	16.99	16.94
1-Diethylamino-2-(2,4-dinitrophenyl)-propane	$C_{13}H_{19}N_3O_4$	55.50	55.40	6.81	6.71	14.94	14.58
Ethyl 2-Diethylamino-1-nitropropionate	$C_9H_{18}N_2O_4$	49.53	49.35	8.31	8.21	12.84	12.73

SECTION III

STUDY OF THE EFFECT OF ACID CONCENTRATION ON THE PREPARATION OF THE MANNICH BASE, 1-DIETHYLAMINO-2-METHYL-2-NITROPROPANE

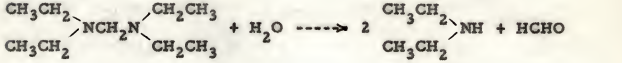
A. Discussion

In all cases where the amine hydrochloride or ammonium chloride is used in the Mannich reaction, the active hydrogen compound has been an aldehyde, ketone, or some other compound which has a carbonyl group to activate the hydrogen on the adjacent carbon. This experiment was designed to show whether or not active hydrogen compounds which did not contain a carbonyl group would also be catalyzed by a mineral acid. If, as was found, the reaction was not catalyzed by acid, it would appear that the reaction mechanism was different in the two cases.

Although there was a decided decrease in yield as the acid concentration was increased, the yield of 1-diethylamino-2-methyl-2-nitropropane did not become zero. In the procedure used, it was necessary to dry the material obtained in the reaction overnight with "Drierite" before distilling. Thus it was possible for the reaction to

continue at room temperature. That the reaction was able to proceed at room temperature was shown by the fact that when 0.2 moles of tetraethylmethylenediamine and 0.2 moles of 2-nitropropane were mixed together and allowed to stand for twenty-one hours and fifteen minutes, a yield of 89.9% of the Mannich base was obtained on vacuum distillation.

Attempts to use tetraethylmethylenediamine dihydrochloride in this study were unsuccessful since the compound is not stable and is extremely hygroscopic. On standing the tetraethylmethylenediamine dihydrochloride quickly became a solution by absorption of moisture and hydrolyzed to free formaldehyde and diethylamine hydrochloride. The odor of formaldehyde was easily detected during this time. The solution was allowed to remain open to the air for several days, resulting in evaporation of the moisture and formaldehyde and leaving the white diethylamine hydrochloride.



B. Experimental

Preparation of 1-Diethylamino-2-methyl-2-nitropropane in Acid Solution

In a 200 ml., round-bottomed, three-necked flask equipped with a mechanical stirrer and a condenser were placed 31.7 gms. of

tetraethylmethylenediamine (0.2 mole), 17.8 gms. of 2-nitropropane (0.2 mole), 9 ml. of concentrated hydrochloric acid (0.1 mole), and 31 ml. of water. In subsequent reactions, 18 ml. of concentrated hydrochloric acid (0.2 mole) with 22 ml. of water, 27 ml. of concentrated hydrochloric acid (0.3 mole) with 13 ml. of water, and 36 ml. of hydrochloric acid (0.4 mole) with 4 ml. of water were used. This reaction mixture was heated on the steam bath with stirring for a period of three hours. The organic layer was separated mechanically from the aqueous layer. The water layer was extracted three times with benzene which was added to the organic layer. The combined organic materials were then dried overnight with "Drierite." Distillation of the benzene and the diethylamine formed in the reaction was carried out at atmospheric pressure. The 1-diethylamino-2-methyl-2-nitropropane was distilled under vacuum (b. 91-2°/10 mm.).

TABLE II

EFFECT OF ACID CONCENTRATION ON YIELD OF 1-DIETHYLAMINO-2-METHYL-2-NITROPROPANE

Moles of Acid	Per Cent Yield			
	#1	#2	#3	Av.
0.1	83.4	87.6	82.3	84.4
0.2	78.2	75.0	75.8	76.3
0.3	45.4	46.8	58.7	50.3
0.4	31.1	8.6	25.0	21.6

Preparation of Tetraethylmethylenediamine Dihydrochloride

A dilute solution of tetraethylmethylenediamine in dry ether was prepared in an Erlenmeyer flask. The solution was cooled in an ice bath while hydrogen chloride was bubbled through it. A white crystalline solid was formed which was collected by filtering, and then placed on a watch glass to air dry.

After several minutes, the solid was covered with water, thus indicating that the product was hygroscopic. Several hours later, the equilibrium mixture between the solid and liquid gave off a strong odor of formaldehyde, which indicated that the product was being hydrolyzed. Over a period of twenty-four hours, the material in the watch glass

became completely liquid, and the odor of formaldehyde became increasingly difficult to detect. Two days after the tetraethylmethylenediamine dihydrochloride had been prepared, all of the water had evaporated leaving a white solid. This was dried in the 100° oven for fifteen minutes. This compound melted at 223-4° (uncorr.) while the literature gives the melting point of diethylamine hydrochloride as 228-9°.

SECTION IV

A STUDY OF THE EFFECT OF HYDROGEN CHLORIDE IN ETHANOL ON THE PREPARATION OF 1-DIETHYLAMINO-2-METHYL-2-NITROPROPANE

A. Discussion

It has previously been shown that when working in aqueous solvents, the yield of 1-diethylamino-2-methyl-2-nitropropane from tetraethylmethylenediamine and 2-nitropropane decreased as the hydrogen chloride concentration increased. McLeod and Robinson[18] isolated ethers of the type R_2NCH_2OR from secondary amines, formaldehyde, and alcohol. These ethers would then condense with active hydrogen compounds. Thus, it would appear that the ethers are possible intermediates in the Mannich reaction where alcohols are used as solvents.

A comparison of the results in Table III with those shown in Table II on page 19 which were obtained from similar experiments carried out in aqueous solution, indicates that the ethers mentioned above may play an important role in the Mannich reaction when alcohols are used as solvents. This is also indicated from the literature, since

TABLE III

EFFECT OF HYDROGEN CHLORIDE IN ETHANOL ON YIELD OF 1-DIETHYLAMINO-2-METHYL-2-NITROPROPANE

Moles of HCl	Per Cent Product Obtained		
	I	II	Av.
0.0	82.2	80.7	81.4
0.1	76.8	53.2	65.0
0.2	64.2	70.5	62.4
0.3	67.0	56.7	61.8
0.4	59.0	63.6	57.7

in most cases in which the amine salt was used as a reactant, an alcohol was used as the solvent.

B. Experimental

In a 200 ml., three-necked, round-bottomed flask equipped with a mechanical stirrer and a condenser was placed 100 ml. of alcoholic hydrogen chloride (0.4 mole). In subsequent reactions, the amount of hydrogen chloride present was decreased to 0.3, 0.2, 0.1, and finally 0.0 moles. To this, 31.7 gms. of tetraethylmethylenediamine (0.2 mole) was carefully added. When all of the amine had been added, 17.8 gms. of 2-nitropropane (0.2 mole) was introduced into the reaction

flask. Stirring while heating was then carried out over a four hour period. On cooling, the amine hydrochloride was salted out with ether. In all cases this was found to consist entirely of diethylamine hydrochloride. The product was then obtained by distilling the ether-alcohol-amine solution.

SECTION V

STUDY OF THE REACTION BETWEEN TETRAETHYLMETHYLENEDIAMINE AND 2-METHYL-2-NITRO-1-PROPANOL USING CARBON-14

A. Discussion

Senkus[8] and Johnson[9] were able to produce the same Mannich base by means of two different reaction series. Thus, according to their reaction sequences, if diethylamine were reacted with formaldehyde to form tetraethylmethylenediamine, and if this were in turn reacted with 2-nitropropane, the Mannich base 1-diethylamino-2-methyl-2-nitropropane would result. Or, if 2-nitropropane were reacted with formaldehyde to form 2-methyl-2-nitro-1-propanol, and if this were in turn reacted with diethylamine, the Mannich base 1-diethylamine-2-methyl-2-nitropropane would again result.

Johnson[9] suggested that when a nitroalcohol was used, the first step would be its breaking down into formaldehyde and the nitroparaffin which in this case would be 2-nitropropane. By the use of formaldehyde-C^{14} it should be possible to test the validity of

his suggestion.

B. Synthesis of Radioactive Starting Materials

Preparation of Tetraethylmethylenediamine-methyleneyl-C^{14}

Eight grams of diethylamine (0.11 mole) was placed in a 25 ml., cone-shaped, three-necked flask equipped with a reflux condenser and an addition funnel. By means of a hypodermic syringe, 1.0 ml. of formaldehyde-C^{14} (0.1 millimole, 0.1 millicurie) was added. The syringe was washed out with 3.7 ml. of formalin (0.05 mole) which was placed in the addition funnel. This formaldehyde was added dropwise at a slow rate. Stirring, by means of a magnetic stirrer, was carried out during the addition and for a six hour period following. The reaction mixture was then allowed to stand overnight. After mechanically separating the reaction mixture, the aqueous portion was extracted with three 5 ml. portions of benzene which were combined with the organic layer. Distillation at atmospheric pressure yielded 6.6071 gms. (83.5%) of tetraethylmethylenediamine-methyleneyl-C^{14}.

Analysis:

Sample		=	4.0 mg.
Weight of $BaCO_3$		=	46.8 mg.
Blank		=	2.5 mg.
			44.3 mg.
Counts	12(512) + 255		(one minute)
	12(512) + 248		
	12(512) + 187		
	12(512) + 122		
Average Counts		=	6344 dpm
		=	105.73 dps
Background		=	1.78 dps
			103.95 dps
Efficiency		=	0.170
Counts (100%)		=	611.4 dps
Specific Activity		=	152.9dps/mg.
Total Activity		=	1.010×10^6 dps
		=	27.30 microcuries

Preparation of
2-Methyl-2-nitro-1-propanol-C^{14}

In a 25 ml., three-necked, pear-shaped flask equipped with a mechanical stirrer and a reflux condenser were place 8.9 gms. of 2-nitropropane (0.1 mole) and 0.8 gms. of sodium bicarbonate. One

milliliter of formaldehyde-C^{14} (0.1 millimole, 0.1 millicurie) was measured out and added to the reaction flask by means of a hypodermic syringe. The syringe was washed out by running 7.8 ml. of formalin through it into the reaction flask. Heating, by means of a Glas-Col heating mantle, was carried out with stirring over a four hour period. The resulting solution was dried to a yellow-white solid under vacuum. Vacuum distillation of this solid yielded 8.3814 gms. (70.4%) of a white crystalline solid.

Analysis:

Sample	=	3.2 mg.
Weight of $BaCO_3$	=	25.1 mg.
Blank	=	3.1 mg.
		22.0 mg.
Counts 8(512) + 352		(one minute)
8(512) + 367		
Average Counts	=	4456 dpm
	=	74.27 dps
Background	=	1.32 dps
		72.95 dps
Efficiency	=	0.233
Counts (100%)	=	315.1 dps

Specific Activity = 97.84 dps/mg.

Total Activity = 8.200×10^5 dps.

= 22.16 microcuries

C. Synthesis of 1-Diethylamino-2-methyl-2-nitropropane-1-C^{14}

Reaction of Tetraethylmethylenediamine-methyleneyl-C^{14} with 2-Methyl-2-nitro-1-propanol

In a 25 ml., three-necked, pear-shaped flask equipped with a mechanical stirrer and a reflux condenser were placed 6.2129 gms. of tetraethylmethylenediamine-methyleneyl-C^{14} (0.0393 mole, 25.53 microcuries) and 4.7 gms. of 2-methyl-2-nitro-1-propanol. A cold trap, containing two milliliters of ethanol and immersed in a Dry Ice-acetone freezing mixture, was connected to the top of the reflux condenser by means of a short rubber tube. This was used to prevent the escape of any free formaldehyde during the reaction. Heating, by means of a Glas-Col heating mantle, with stirring was carried out over a three hour period. The next day the water layer was separated mechanically and extracted twice with small portions of benzene. The laboratory monitor did not show the presence of any radioactivity in the remaining aqueous material. The combined benzene extract and organic layer were distilled.

From the forerun, a yield of 6.0928 gms. of material was obtained between 35° and 80°. The second fraction consisting of

1.3186 gms. of tetraethylmethylenediamine was obtained at 78-80° / 30 mm. The third fraction yielded 5.2908 gms. (77.4%) of 1-diethylamino-2-methyl-2-nitropropane at 90-92° /10 mm. Four grams of material were obtained from the cold trap. In the distilling pot there remained 0.5143 gms. of a carbonaceous material.

The alcohol-formaldehyde solution in the cold trap was treated with 2,4-dinitrophenylhydrazine. This resulted in 0.9053 gms. of a dinitrophenylhydrazine-dinitrophenyl-hydrazone mixture which could be plated on an aluminum planchet and counted directly.

Analysis:

(1) Dinitrophenylhydrazine-dinitrophenylhydrazone Mixture

Sample	=	2.49 mg.
Counts (five minutes)	3(512) + 250	
	3(512) + 238	
Average Count	=	1780 d/5m
	=	5.93 dps
Background	=	1.78 dps
		4.15 dps
Efficiency	=	0.490
Counts (100%)	=	8.469 dps

Specific Activity = 3.401 dps/mg.

Total Activity = 2.358×10^3 dps

= 0.06 microcuries

(2) Forerun

Sample = 4.9 mg.

Weight of $BaCO_3$ = 29.5 mg.

Blank = 2.5 mg.

27.0 mg.

Counts (five minutes) 10(128) + 48

10(128) + 77

Average Count = 1342 d/5m

= 4.47 dps

Background = 1.32 dps

3.15 dps

Efficiency = 0.205

Counts (100%) = 15.37 dps

Specific Activity = 3.136 dps/mg.

Total Activity = 1.911×10^4 dps

= 0.52 microcuries

(3) Tetraethylmethylenediamine

Sample	=	4.3 mg.
Weight of $BaCO_3$	=	47.7 mg.
Blank	=	2.5 mg.
		45.2 mg.
Counts (five minutes)	7(512)	+ 446
	7(512)	+ 437
Average Count	=	4044 d/5m
	=	13.48 dps
Background	=	1.32 dps
		12.16 dps
Efficiency	=	0.170
Counts (100%)	=	71.53 dps
Specific Activity	=	16.63 dps/mg.
Total Activity	=	2.193×10^4 dps
	=	0.59 microcuries

(4) 1-Diethylamino-2-methyl-2-nitropropane

Sample	=	5.0 mg.
Weight of $BaCO_3$	=	47.2 mg.
Blank	=	2.5 mg.
		44.7 mg.

Counts (one minute)	10(512) + 248	
	10(512) + 323	
Average Count	= 5406 dpm	
	= 90.10 dps	
Background	= 1.32 dps	
	88.78 dps	
Efficiency	= 0.170	
Counts (100%)	= 522.2 dps	
Specific Activity	= 104.4 dps/mg.	
Total Activity	= 5.526×10^5 dps	
	= 14.94 microcuries	

(5) Cold Trap

Sample	= 4.1 mg.	
Weight of $BaCO_3$	= 45.8 mg.	
Blank	= 2.5 mg.	
	43.3 mg.	
Counts (five minutes)	17(512) + 326	
	17(512) + 106	
Average Count	= 8920 d/5m	
	= 29.73 dps	
Background	= 1.32 dps	
	28.41 dps	

Efficiency	= 0.170
Counts (100%)	= 167.7 dps
Specific Activity	= 40.90 dps/mg.
Total Activity	= 1.636×10^5 dps
	= 4.42 microcuries

(6) Carbonaceous residue

Sample	= 4.9 mg.
Weight of $BaCO_3$	= 49.1 mg.
Blank	= 2.5 mg.
	46.6 mg.
Counts (one minute)	23(512) + 50
	22(512) +380
	22(512) +434
Average Count	= 11,722 dpm
	= 195.37 dps
Background	= 1.32 dps
	194.05 dps
Efficiency	= 0.170
Counts (100%)	= 1141 dps
Specific Activity	= 232.7 dps/mg.
Total Activity	= 1.198×10^5 dps
	= 3.24 microcuries

Reaction of 2-Methyl-2-nitro-1-propanol-1-C^{14} with Tetraethylmethylenediamine

The following reaction was run exactly as the previous reaction. In this run, 8.3814 gms. of 2-methyl-2-nitro-1-propanol-1-C^{14} (0.0704 mole, 22.16 microcuries) was reacted with 11.1 gms. of tetraethylmethylenediamine (0.0704 moles).

On distillation, the forerun which was collected between 35° and 80° contained 13.8441 gms. of material. The second cut consisting of 2.9459 gms. of tetraethylmethylenediamine was collected at 78-80°/30 mm. The third fraction consisted of 10.8521 gms. (88.47%) of 1-diethylamino-2-methyl-2-nitropropane which was collected at 90-92°/10 mm. The cold trap contained 6.1 gms. of material. There remained 0.4824 gms. of carbonaceous material in the distilling pot.

Analysis:

(1) Dinitrophenylhydrazine-Dinitrophenylhydrazone Mixture

Sample	=	2.62 mg.
Counts (five minutes)	2(512) + 328	
	2(512) + 303	
Average Count	=	1340 d/5m
	=	4.47 dps
Background	=	1.48 dps
		2.99 dps
Efficiency	=	0.490

Counts (100%) = 6.102 dps

Specific Activity = 2.329 dps/mg.

Total Activity = 2.108×10^3 dps

= 0.06 microcuries

(2) Forerun

Sample = 5.9 mg.

Weight of $BaCO_3$ = 42.9 mg.

Blank = 3.1 mg.

39.8 mg.

Counts (five minutes) 3(256) + 195

3(256) + 176

Average Count = 954 d/5m

= 3.18 dps

Background = 1.32 dps

1.86 dps

Efficiency = 0.170

Counts (100%) = 10.94 dps

Specific Activity = 1.854 dps/mg.

Total Activity = 2.567×10^4 dps

= 0.69 microcuries

(3) Tetraethylmethylenediamine

Sample	=	4.2 mg.
Weight of $BaCO_3$	=	44.4 mg.
Blank	=	3.1 mg.
		41.3 mg.
Counts (one minute)	14(512) + 68	
	14(512) +249	
Average Count	=	7326 dpm
	=	122.10 dps
Background	=	1.32 dps
		120.78 dps
Efficiency	=	0.172
Counts (100%)	=	710.5 dps
Specific Activity	=	169.2 dps/mg.
Total Activity	=	4.983×10^5 dps
	=	13.47 microcuries

(4) 1-Diethylamino-2-methyl-2-nitropropane

Sample	=	7.9 mg.
Weight of $BaCO_3$	=	79.9 mg.
Blank	=	3.1 mg.
		76.8 mg.

Counts (five minutes) 24(512) + 36

24(512) + 423

Average Count = 12,262 d/5m

= 40.82 dps

Background = 1.32 dps

39.50 dps

Efficiency = 0.170

Counts (100%) = 232.4 dps

Specific Activity = 29.41 dps/mg.

Total Activity = 1.794×10^5 dps

= 4.85 microcuries

(5) Cold Trap

Sample = 4.1 mg.

Weight of $BaCO_3$ = 45.0 mg.

Blank = 3.1 mg.

41.9 mg.

Counts (five minutes) 6(512) + 236

6(512) + 77

Average Count = 3228 d/5m

= 10.76 dps

Background = 1.32 dps

9.44 dps

Efficiency	=	0.170
Counts (100%)	=	55.53 dps
Specific Activity	=	13.54 dps/mg.
Total Activity	=	8.262×10^4 dps
	=	2.23 microcuries

(6) Carbonaceous Residue

Sample	=	8.1 mg.
Weight of $BaCO_3$	=	76.4 mg.
Blank	=	3.1 mg.
		73.3 mg.
Counts (one minute)	8(512) + 411	
	8(512) + 127	
	8(512) + 200	
	8(512) + 65	
Average Count	=	4297 dpm
	=	71.62 dps
Background	=	1.32 dps
		70.30 dps
Efficiency	=	0.170
Counts (100%)	=	413.5 dps
Specific Activity	=	51.05 dps/mg.

Total Activity = 2.463×10^4 dps

= 0.67 microcuries

TABLE IV

RADIOACTIVE ANALYSIS OF THE DISTILLATION FRACTIONS OBTAINED FROM THE REACTION OF TETRAETHYLMETHYLENEDIAMINE-METHYLENEYL-C^{14} WITH 2-METHYL-2-NITRO-1-PROPANOL

	Sp. Act. (dps/mg.)	Total Act. (microcuries)	Act./Mole (microcuries/mole)
Forerun	3.136	0.52	-----
Tetraethylmethylene-diamine	16.63	0.59	71.14
1-Diethylamino-2-methyl-2-nitropropane	104.4	14.94	491.64
Cold Trap	40.90	4.42	-----
Carbonaceous Residue	232.7	3.24	-----

TABLE V

RADIOACTIVE ANALYSIS OF THE DISTILLATION FRACTIONS OBTAINED FROM THE REACTION OF 2-METHYL-2-NITRO-1-PROPANOL-1-C^{14} WITH TETRAETHYLMETHYLENEDIAMINE

	Sp. Act. (dps/mg.)	Total Act. (microcuries)	Act./Mole (microcuries/mole)
Forerun	1.854	0.69	-----
Tetraethylmethylene-diamine	169.2	13.47	723.86
1-Diethylamino-2-methyl-2-nitropropane	29.41	4.85	138.50
Cold Trap	13.54	2.23	-----
Carbonaceous Residue	51.05	0.67	-----

SECTION VI

CARBONATE METHOD OF ANALYSIS FOR RADIOACTIVITY

A. Oxidation of Sample

A small sample of the radioactive compound was weighed directly into the combustion tube. To this was added 200 mg. of powdered potassium iodate which aids in the oxidation of the organic material. The carbon dioxide was collected in two milliliters of a sodium hydroxide solution containing hydrazine sulfate. This solution was prepared by mixing 100 ml. of 1N sodium hydroxide with two grams of hydrazine sulfate. This solution loses strength, so that it may not be kept over one month.

The oxidation apparatus had the shape of an "h." On the left side there was a dropping funnel for the addition of the Van Slyke oxidizing mixture. The funnel could be cut off from the rest of the apparatus by means of a glass stopcock. A three-way stopcock divided the apparatus in half and was the point from which it was evacuated. The oxidation tube, which contained an inside 19/38 T joint, is connected to the apparatus below the addition funnel. At the other end a 50 ml. Erlenmeyer flask which had an outside 19/38 T joint is

attached. In this flask was placed the sodium hydroxide solution described above.

The Van Slyke oxidation mixture was made up in a one liter glass-stoppered Erlenmeyer flask. In this was placed 25 gms. of chromium trioxide, 167 ml. of phosphoric acid (density 1.7), and 333 ml. of fuming sulfuric acid containing 20% free sulfur trioxide. The mixture was heated on a hot plate with stirring until the temperature of the solution reached 150°. This was done so that all of the solids could be put into solution. On cooling, the flask was stoppered, and the oxidation mixture was ready for use.

After the oxidation tube and the Erlenmeyer flask had been attached to the oxidation flask, the liquid contents were solidified by means of a Dry Ice-isopropanol freezing mixture. The apparatus was then evacuated by means of a vacuum pump. A vacuum of approximately one millimeter was achieved. The apparatus was then sealed off, and the vacuum pump was disconnected. Two milliliters of the Van Slyke oxidizing mixture was carefully added dropwise. Gentle heating with a burner was carried out over a 15 minute period. In order to drive over any remaining carbon dioxide, the oxidizing solution was boiled vigorously, and at the same time, the receiver was again immersed in the freezing mixture. By means of the three-way stopcock, the receiver was then sealed off from the rest of the apparatus.

B. Precipitation as Barium Carbonate

The apparatus used in precipitating the barium carbonate differed from the wet combustion apparatus only in that the two halves were not separated by a stopcock. Instead, evacuation of the apparatus was accomplished by means of a side tube containing a stopcock and attached at the mid-point of the cross tube. The Erlenmeyer flask which now contained a sodium hydroxide-sodium carbonate mixture was, after the addition of one drop of methyl orange, attached to the apparatus under the dropping funnel. An approximately 25 ml. Erlenmeyer flask containing two milliliters of a barium hydroxide-barium chloride solution, was attached at the other end. The precipitating solution was prepared by adding 160 ml. of a barium chloride solution containing 12 gms. of $BaCl_2 \cdot 2H_2O$ per 100 ml. of water to 800 ml. of a saturated solution of barium hydroxide.

The liquids in the apparatus were frozen, and the system was evacuated as previously described. After the system had been sealed off and the pump disconnected, several drops of dilute sulfuric acid were added to the sodium hydroxide-sodium carbonate solution. This was then heated for several minutes by means of a water bath. Just before the heating was to be discontinued, the barium hydroxide-barium chloride solution was again frozen as an aid in pulling over any free carbon dioxide remaining in the system.

After the barium hydroxide-barium chloride solution had melted,

it was allowed to stand for at least twenty minutes under vacuum before filtering. A special stainless steel precipitator was used for collecting the barium carbonate. This consisted of two pieces. The bottom was a disc with drains in it and the filter paper was placed on this. The other piece was a hollow cylinder which holds the filter paper tightly on the disc. The precipitate was rapidly filtered by suction, washed several times with water, and then washed with alcohol. The filter paper containing the barium carbonate disc is removed from the precipitator and dried in the oven at 110° for one hour. The precipitator used in this work made a barium carbonate disc which had an area of 2.895 cm^2.

The efficiency of the counting was determined from the thickness of the barium carbonate disc in milligrams per square centimeter. Yankwich and Weigl[24] have worked out a table of efficiencies for the corresponding barium carbonate thicknesses. The actual counting was done on a proportional counter.

SECTION VII

ATTEMPTED KINETIC STUDIES OF THE REACTION OF ACTIVE HYDROGEN COMPOUNDS WITH TETRAETHYLMETHYLENEDIAMINE

A. Discussion

Many attempts were made to elucidate the kinetics of the Mannich reaction without success. It was thought that the kinetics of the reaction of 2-nitropropane with tetraethylmethylenediamine in cyclohexane could be determined by measuring the decrease in the concentration of 2-nitropropane as the reaction proceeded. This was done by extracting all of the amines out of solution with concentrated hydrochloric acid, and then measuring the optical density of the remaining 2-nitropropane-cyclohexane solution. Although this experiment did not result in obtaining the desired kinetic results due to the solubility of 2-nitropropane in water, the procedure was believed to be a good one.

The kinetics of the reaction between 2-nitropropane and tetraethylmethylenediamine in an aqueous system could not be determined by means of the change in pH. There was no significant change in the

pH between the start and completion of the reaction. Similar results were observed when an attempt was made to use the change in the refractive index as a means of measuring the kinetics of the reaction. The difference between the initial and final reading was only 0.0049. Another method which was tried was that of precipitating the diethylamine formed in the reaction from the cyclohexane solution with benzenesulfonyl chloride. After 108 hours there was no significant increase in the amount of diethylamine produced in the reaction. It would appear that a quantitative precipitation of N, N'-diethylbenzenesulfonamide was not obtained.

Quantitative data could not be obtained from infrared spectra on the reaction of 2-nitropropane with tetraethylmethylenediamine in cyclohexane. Measuring the concentration of the diethylamine by means of the 13.90 micron band showed that the concentration, as the reaction proceeded, was becoming increasingly larger than the concentration to be expected at the completion of the reaction. This was explained when infrared curves were run on mono-, di-, and tri-n-hexylamine. It was found that tertiary amines also absorb in the same region as the secondary amines and thus produce an additive effect. It has also been noted that infrared curves of all the Mannich bases that have been prepared here absorb between 5.95 and 6.00 microns. Unfortunately this band was too sharp as well as too weak to be used for quantitative determinations.

Radioactive diphenylacetonitrile was prepared for use as the active hydrogen compound in the reaction with tetraethylmethylenediamine. The reaction was run in toluene. The amines were extracted with concentrated hydrochloric acid, and the specific activity of the resulting solution was determined. The data obtained in this experiment were of no value. One reason for this was the low activity of the solution due to the dilution effect of the toluene. It would also appear that some hydrolysis of the nitrile group occurred during the extraction of the amines.

B. Experimental

Determination of Optical Density at Various Concentrations of 2-Nitropropane in Cyclohexane

Thirteen different concentrations of 2-nitropropane in cyclohexane were run on the Beckman Model DU spectrophotometer between 240 millimicrons and 350 millimicrons. As this range was in the ultraviolet, it was necessary to use quartz cells. The pure solvent was placed in the 1.002 cm. cell, and the solution was placed in the 1.000 cm. cell. The per cent transmission of each concentration was then plotted *versus* the wave length. It was found that each curve passed through a minimum at 280 millimicrons. This point was then selected for the plotting of the concentration *versus* optical density.

Table VI lists the optical density for each concentration at 280 millimicrons.

TABLE VI

OPTICAL DENSITY OF 2-NITROPROPANE IN CYCLOHEXANE

Molar Concentration	Optical Density
1.012×10^{-1}	2.39
7.084×10^{-2}	1.79
5.060×10^{-2}	1.40
3.036×10^{-2}	1.09
1.012×10^{-2}	0.598
7.084×10^{-3}	0.549
5.060×10^{-3}	0.507
3.036×10^{-3}	0.166
1.012×10^{-3}	0.155
7.084×10^{-4}	0.148
5.060×10^{-4}	0.108
3.036×10^{-4}	0.067
1.012×10^{-4}	0.067

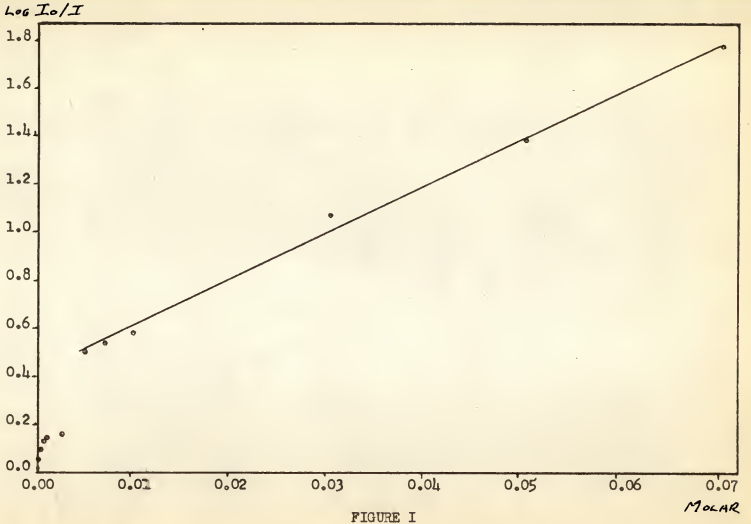


FIGURE I

Graph of the Relationship of the Optical Density with the Concentration of 2-Nitropropane in Cyclohexane at 280 Millimicrons

Attempted Kinetic Study Using a Spectrophotometer

Eight and nine-tenths grams of 2-nitropropane (0.1 mole) was placed in a one liter volumetric flask and brought up to volume with cyclohexane. To this was added 15.8 gms. of tetraethylmethylenediamine (0.1 mole). After shaking the solution to insure homogeneity, a ten milliliter sample was withdrawn. This was treated in the following manner. First it was extracted with one milliliter of concentrated hydrochloric acid, then washed with water, extracted again with one milliliter of concentrated hydrochloric acid, washed twice more with water, and then dried over calcium chloride. The optical density of the solution was determined at 280 millimicrons. This work was carried out in the 24° C. constant temperature room. The results are listed in Table VII.

TABLE VII

DATA ON KINETIC STUDY USING SPECTROPHOTOMETER

Time in Hours	Optical Density	Molar Concentration
0:00	0.980	0.0290
1:00	0.639	0.0139
2:00	0.899	0.0252
3:00	1.19	0.0397
5:00	1.23	0.0417
7:00	0.820	0.0206
9:00	0.840	0.0215
11:00	1.13	0.0367
14:00	0.884	0.0240
26:00	0.918	0.0258
38:00	1.01	0.0300

Attempted Kinetic Study Using the Change in pH

Eight and nine-tenths grams of 2-nitropropane (0.1 mole), and 100 ml. of water were placed in a 200 ml., round-bottomed, three-necked flask equipped with calomel and glass high temperature electrodes and a reflux condenser with a thermometer which extended down

into the liquid in the flask. The reaction was stirred by means of a magnetic stirrer and heated by means of a Glas-Col heating mantle. When the pot temperature had reached 84°, 15.8 gms. of tetraethylmethylenediamine (0.1 mole) was added through the top of the condenser. As soon as the materials were mixed, stirring was stopped and the pH was determined. Thereafter, stirring was stopped 20 seconds before each reading was taken. The results are listed in Table VIII.

TABLE VIII

DATA ON KINETIC STUDY USING CHANGE IN pH

Temperature in ° C.	Time in Hours	pH
81	0:00	0.00
88	0:05	0.02
89	0:10	0.35
91	0:15	0.42
91	0:20	0.52
91	0:25	0.80
91	0.30	0.67
88	0:40	0.92
89	0:50	0.98
88	1:00	1.20
88	1:15	1.10
88	1:45	1.14
88	2:15	1.10
88	2:45	1.03

The experiment was repeated at 24° using a blue glass electrode and an ordinary calomel electrode in place of the high temperature

electrodes. Stirring was discontinued one-half minute before each reading. The results are given in Table IX.

TABLE IX

DATA ON KINETIC STUDY USING CHANGE IN pH

Time in Hours	pH
0:00	0.00
0:10	-0.10
0:40	-0.12
1:10	-0.10
2:10	-0.18
4:10	-0.13
6:40	-0.16

Attempted Kinetic Study by Precipitating Diethylamine with Benzenesulfonyl Chloride

In a 500 ml. volumetric flask were placed 7.989 gms. of tetraethylmethylenediamine (0.0505 mole) and 5.0 ml. of 2-nitropropane (0.055 mole). The mixture was brought up to volume with cyclohexane. At definite intervals a 25.0 ml. sample was withdrawn and cooled in an ice bath. The diethylamine present in the solution

was then precipitated with benzenesulfonyl chloride. After ten minutes of intermittent shaking, the solid was collected on a previously weighed sintered glass crucible. The results are listed in Table X.

TABLE X

DATA ON KINETIC STUDY USING PRECIPITATION OF DIETHYLAMINE

Time in Hours	Moles of Diethylamine
1:00	0.001439
2:00	0.001447
3:00	0.001436
4:00	0.001433
5:00	0.001444
108:00	0.001453

Determination of Optical Density at Various Concentrations of Diethylamine in Cyclohexane

Five known concentrations of diethylamine in cyclohexane were run on the infrared spectrophotometer in one millimeter and three millimeter cells. The optical density was then plotted against the concentration. The results are given in Table XI. The results

obtained by using the three millimeter cell followed Beer's law.

TABLE XI

OPTICAL DENSITY OF DIETHYLAMINE IN CYCLOHEXANE

Molar Concentration	Optical Density	
	1 mm. cell	3 mm. cell
0.107	9.54	-----
0.0535	1.88	5.52
0.0107	1.38	1.95
0.00535	1.25	1.40
0.00107	----	1.08

Attempted Kinetic Study Using Infrared Spectra

In a 250 ml. volumetric flask were placed 1.9786 gms. of tetraethylmethylenediamine and 1.1 ml. of 2-nitropropane. The resulting mixture was brought up to volume with cyclohexane. After nine hours and nineteen minutes, the concentration of diethylamine, as calculated from the optical density, was greater than 0.05M, the limiting value.

Preparation of Benzyl Cyanide-C^{14}

Six and three-tenths grams of benzyl chloride (0.05 mole), 3.1 gms. of sodium cyanide (0.06 mole), 2.0 ml. of sodium cyanide-C^{14} (0.2 millicuries), 0.8 ml. of water, and 6.2 gms. of ethanol were placed in a 25 ml., pear-shaped, three-necked flask equipped with a reflux condenser and a mechanical stirrer. Heating, by means of a Glas Col heating mantle, and stirring were carried out over a four hour period. On cooling, the material was filtered by suction to remove most of the sodium chloride. The filtered salt was washed with a small portion of alcohol. The alcohol was removed by distillated at atmospheric pressure. Any remaining alcohol or water were removed with the aspirator. Vacuum distillation of the remaining material yielded 4.0 gms. (68.4%) of product at 110-12° /13 mm.

Preparation of Diphenylacetonitrile-cyano-C^{14}

In a 25 ml., pear-shaped, three-necked flask equipped with an air condenser, an addition funnel, and a mechanical stirrer was placed 11.7 gms. of benzyl cyanide-C^{14} (0.1 mole). The benzyl cyanide-C^{14} was heated to 105° by means of a Glas Col heating mantle with stirring. Five and seven-tenths milliliters of bromine (0.11 mole) was slowly added dropwise. Heating was discontinued fifteen minutes after the last addition of bromine had been made. Nitrogen, dried by

bubbling through concentrated sulfuric acid, was blown across the surface of the stirred liquid for one hour.

In the next step, 13.4 gms. of aluminum chloride and 36.8 gms. of benzene were placed in a 200 ml., round-bottomed, three-necked flask equipped with a reflux condenser, an addition funnel, and a mechanical stirrer. The alpha-bromo-alpha-phenylacetonitrile-cyano-C^{14} was washed into the addition funnel with ten grams of benzene. The material in the reaction flask was heated to vigorous refluxing on the steam bath with stirring. Careful additions of the alpha-bromo-alpha-phenylacetonitrile-cyano-C^{14} were made in small increments to the boiling solution. After the last addition had been made, the material was allowed to reflux for an additional hour. On cooling, the material was poured into 100 gms. of ice and 10 ml. of concentrated hydrochloric acid. The benzene layer was separated mechanically. The aqueous portion was extracted twice with 25 ml. portions of ether, and the ether extracts were added to the benzene portion. This organic material was washed once with 50 ml. of water and then dried overnight with anhydrous sodium sulfate.

The solvent was removed by distilling at atmospheric pressure until the temperature of the distilling pot reached 110°. The remainder of the solvent was removed by means of an aspirator leaving a brown solid in the pot. This was distilled under vacuum through a Claisen head to which the receiver was attached by means of an adapter. The

product boiled at 122-6° /1-2 mm. and crystallized to a yellow solid. On recrystallization from isopropanol followed by washing with cold isopropanol on a Buchner funnel, 8.9 gms. of product (46.2%) was obtained.

Attempted Kinetic Study Using Carbon-^{14}

In a 250 ml. volumetric flask were placed 4.8 gms. of diphenylacetonitrile-cyano-C^{14} (0.025 mole) and 4.0 gms. of tetraethylmethylenediamine (0.025 mole). This was brought up to volume with toluene. The reaction was carried out in a 37° constant temperature bath. Five ml. samples were removed periodically. These were each extracted with one milliliter of concentrated hydrochloric acid to remove the amines that were present, washed three times with water, and dried over "Drierite." The specific activity of each sample was determined by the barium carbonate method. The results are listed in Table XII.

TABLE XII

DATA ON KINETIC STUDY USING CARBON-14

Time in Hours	Specific Activity in dps/mg.
0:00	0.287
5:30	0.356
9:30	0.990
22:30	0.690
27:30	0.285
34:30	0.781
130:30	0.248

SECTION VIII

DISCUSSION OF RESULTS

Johnson[9] has suggested that the first step when nitroalcohols were used would be the breaking down of the nitroalcohol into formaldehyde and the nitroparaffin. This would then be followed by reaction of the amine with the formaldehyde. This was shown to occur by the following two reaction sequences. In the first case, tetraethylmethylenediamine-methyleneyl-C^{14} (25.67 microcuries) was reacted with 2-methyl-2-nitro-1-propanol. A yield of 77.4% of the 1-diethylamino-2-methyl-2-nitropropane-1-C^{14} (14.94 microcuries) was obtained. This represented 58.19% of the starting radioactivity. Schematically this would be as follows

$$(CH_3CH_2)_2NC^*H_2N(CH_2CH_3)_2 + (CH_3)_2CCH_2OH \longrightarrow$$

$$(CH_3CH_2)_2NC^*H_2C(CH_3)_2 + (CH_3CH_2)_2NH + HCH).$$

A secondary reaction would occur between the diethylamine and the formaldehyde to produce tetraethylmethylenediamine. In the second case, 2-methyl-2-nitro-1-propanol-1-C^{14} (22.16 microcuries) was

reacted with tetraethylmethylenediamine. This time an 88.47% yield of 1-diethylamino-2-methyl-2-nitropropane-1-C^{14} (4.85 microcuries) contained 21.89% of the total radioactivity. Schematically this would be as follows

$$(CH_3)_2\overset{NO_2}{\overset{|}{C}}C^*H_2OH + (CH_3CH_2)_2NCH_2N(CH_2CH_3)_2 \longrightarrow$$

$$(CH_3CH_2)_2NCH_2\overset{NO_2}{\overset{|}{C}}(CH_3)_2 + (CH_3CH_2)_2NH + HC^*HO.$$

The fact that some of the radioactivity occurred in the Mannich base probably was due to the formation of some tetraethylmethylenediamine-methyleneyl-C^{14} as soon as the reaction started. This occurred as a result of the secondary reaction between formaldehyde-C^{14} and diethylamine formed in the primary reaction. Thus it would definitely appear to be established that it was the tetraethylmethylenediamine which reacted with the 2-nitropropane, and not the nitroalcohol, 2-methyl-2-nitro-1-propanol, which reacted with the diethylamine.

Combining the results obtained here with those obtained by others in the field, it has been possible to develop a new theory for the mechanism of the reaction between tetraalkylmethylenediamines with active hydrogen compounds. If the formation of the tetraalkyl-methylenediamine or methylol compound was postulated as the first step in the Mannich reaction as was done by Lieberman and Wagner[13]

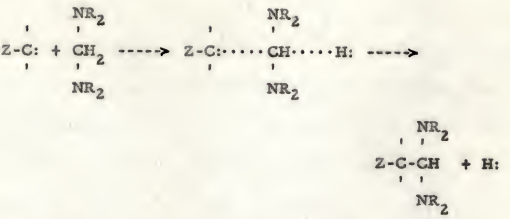
and by Alexander and Underhill,[11] then the mechanism developed here would be that of the Mannich reaction.

The first step in the mechanism for the reaction between tetraalkylmethylenediamine and an active hydrogen compound would be ionization of the active hydrogen compound.

$$Z\text{-}C\text{-}H \text{ ----- } Z\text{-}C\text{:} + H^{+}$$

Evidence for the first step was obtained by reacting 2-nitropropane with tetraethylmethylenediamine in the presence of varying amounts of hydrochloric acid. The results showed that as the hydrogen ion concentration increased, the yield of the Mannich base, 1-diethylamino-2-methyl-2-nitropropane, decreased. This would be predicted from the first step of this theory, since increasing the hydrogen ion concentration would tend to suppress the ionization of the active hydrogen compound.

The second step in the mechanism would be a S_N2 attack by the carbanion on the tetraalkylmethylenediamine with the resulting loss of a hydride ion.



Fernandez[25] was able to obtain kinetic data for the reaction between 2, 4, 6-trinitrotoluene and tetraethylmethylenediamine in toluene. Running the reaction at two different concentrations, it was found that the reaction was second order, first order with respect to 2, 4, 6-trinitrotoluene and tetraethylmethylenediamine. The force of the attack by the carbonium ion would not in itself have sufficient energy to push off a hydride ion. However, the presence of a pair of unshared electrons on the nitrogens in the tetraethylmethylenediamine molecule, would tend to increase the electron density at the methylene group so that a hydride ion conceivably would be pushed off.

Lieberman and Wagner[13] proposed this carbonium ion as the attacking reagent in the Mannich reaction. In the light of present

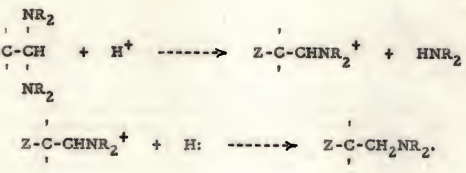
$$R_2NCH_2NR_2 + H^+ \dashrightarrow R_2NH + R_2NCH_2^+$$

knowledge, it does not appear that this could occur. It has been observed that reaction occurs only in those instances in which it is sterically possible for the tetraalkylmethylenediamine and the active hydrogen compound to form a bond. Since the carbonium ion, $R_2NCH_2^+$, is very small in comparison with the tetraalkylmethylenediamine molecule, it would be expected to produce a reaction in a great many more cases than actually occur. This also explains why alcohol is used as a solvent for the Mannich reaction. By reacting the secondary amines, formaldehyde, and alcohol, McLeod and Robinson[18] were able to isolate ethers of the type R_2NCH_2OR' which could be condensed with active hydrogen compounds. Thus these ethers are easier to react than the corresponding tetraalkylmethylenediamine compounds because of their smaller size.

The possibility of a hydride ion coming off was further substantiated by the work of Kharasch and Snyder[26] on the mechanism of the Cannizzaro reaction. In methanol solution where the reaction was not influenced by small amounts of free radical initiators or inhibitors, they interpreted the reaction as involving an intermolecular hydride ion transfer.

In the final step, the dialkylamine is split out leaving a carbonium ion present to react with the hydride ion. Schematically

this would be as follows:



SECTION IX

SUMMARY

Four new Mannich bases have been prepared. They were formed by reacting tetraethylmethylenediamine with the active hydrogen compounds 2-nitropropane, p-nitrophenylacetonitrile, 2,4-dinitroethylbenzene, and ethyl nitroacetate. Analyses were obtained for all four Mannich bases.

By the use of carbon-14, it was possible to demonstrate that when tetraethylmethylenediamine was reacted with 2-methyl-2-nitro-1-propanol, it was the latter which broke down into 2-nitropropane and formaldehyde. It was found that when tetraethylmethylenediamine-methyleneyl-C^{14} was reacted with 2-methyl-2-nitro-1-propanol, the majority of the radioactivity was found in the Mannich base, 1-diethylamino-2-methyl-2-nitropropane. But, when 2-methyl-2-nitro-1-propanol-1-C^{14} was reacted with tetraethylmethylenediamine, only a small fraction of the radioactivity was found in the Mannich base.

A study of the reaction between tetraethylmethylenediamine and 2-nitropropane was made in the presence of varying amounts of hydrogen chloride. Aqueous and alcoholic systems were used. It was

found that the yield of 1-diethylamino-2-methyl-2-nitropropane decreased with increasing hydrogen ion concentration. The decrease was noted to a lesser extent in the alcoholic system.

A mechanism has been proposed for the reaction between active hydrogen compounds and tetraalkylmethylenediamines. If the formation of the tetraalkylmethylenediamine is postulated as the first step in the Mannich reaction, then the mechanism developed here would be that of the Mannich reaction.

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BIOGRAPHICAL ITEMS

Roger A. Johnson was born in Chicago, Illinois, on January 15, 1926. He began his undergraduate work at the University of Illinois in September, 1945.

Mr. Johnson was inducted into the Army in September, 1946 and was honorably discharged in April, 1947. He then returned to the University of Illinois to continue his studies. In September, 1948, he transferred to the University of Florida where he was awarded the degree Bachelor of Science in Chemistry in June, 1950 and the degree Master of Science in February, 1952.

The author has served as an undergraduate research assistant on a United States Naval Research Project at the University of Florida (1949-1950, part-time). He has also served as a graduate assistant (1950-1951) and as a research assistant on an Army Corp of Engineers Research Project at the University of Florida. He was awarded an Army Ordnance Research Fellowship in August, 1952.

Mr. Johnson is a charter member of the Beta Iota chapter of Alpha Chi Sigma, professional chemical fraternity. He is also a member of Gamma Sigma Epsilon, honorary chemical fraternity, and the Society of the Sigma Xi.

This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of the committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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